

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Confirmation No.: 5362

Appl. No. : 10/731,741  
Applicants : Schmitt et al.  
Filed : December 10, 2003  
Title : Cell Preparations Comprising Cells of the T Cell Lineage and  
Methods of Making and Using Same.  
TC./A.U. : 1632  
Examiner : Anoop Kumar Singh  
  
Docket No. : 2223-171  
Customer No. : 001059

**DECLARATION UNDER 37 C.F.R. 1.132**

Honourable Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

Dear Sir:

I, Charles D. Surh citizen of the United States of America and resident of California declare that the following facts are within my knowledge and are true.

1. I am a Professor of Immunology at the Scripps Research Institute. I am a leading authority on the immune system and the role of T lymphocytes. I am especially noted for my work on the selection of young T cells in the thymus and the factors controlling mature T cell survival in the extrathymic environment.

My curriculum vitae is attached as Exhibit A.

2. I have reviewed the above-referenced application (hereinafter "the application") and the Office Action for the application that issued on October 27, 2008.

3. In particular, I note the Examiner's objection the claims as being obvious over a combination of the references Jaleco et al. (2001, J. Exp. Med. 194:991-1001, IDS); Nakano et al. (1994, Science 265:5157 IDS); Pui et al. (Immunity, 1999, 11(3):299-308), and Tatsumi et al. (1990, Proc. Natl. Acad. Sci. 87:2750-2754, IDS). I respectfully disagree with the Examiner for the reasons that follow.

4. It is my utmost professional view that the invention described in the application that OP9-DL1 cells support T cell development is original and its novelty and inventiveness is NOT negated by prior publications. The closest prior art is found in a publication by Jaleco et al in 2001 who claimed that S17-DL1 cells induced differentiation of human cord blood progenitors cells into T cells. Careful examination of this paper, however, reveals that this conclusion is a great over interpretation of their results, mostly contained in Table 1. In their experiments Jaleco et al cultured progenitor cells for up to 6 wks with S17-DL1. Their strongest data are that at 4 and/or 6 wk time points they found cells displaying T cell markers: surface expression of CD7 (76-82%), CD4/8 (2-4%), CD3 (2-4%) and cytoplasmic expression of CD3

(66.2%). I am NOT convinced that any of these data are unequivocally proof of T cell development for the following reasons. First, the starting progenitor cell populations were only 87% pure and contaminated with cells expressing T cell markers (10% CD7, 5% CD3); hence, these contaminating cells could have persisted and expanded over 4-6 wks. The duration of 4-6 wks is also much longer than the 2 wks that is typically required for T cell development in vivo (and in vitro as shown by the inventors' work), indicating that S17-DL-1 cells were extremely inefficient at promoting T cell development and/or contaminating cells expanded during this time. Second, cells expressing immature T cell markers, CD4/8 (2-4%), could reflect activated CD3<sup>+</sup> mature T cells (5% in the starting population), as it is known that activated human T cells often express both CD4 and CD8. Third, surface CD7 and cytoplasmic CD3 expression cannot be used as a T cell-specific marker as human NK cells also express these markers. The only way to circumvent these concerns is to start with highly pure progenitor cells, void of mature T cells, and analyze several T and NK cell markers on the recovered cells by multiple-color staining. Since these approaches were not taken, the data by Jaleco et al cannot be accepted as proof that expression of Delta-1 on stromal cells induces differentiation of progenitor cells into immature T cells. This skepticism is especially relevant in light of many previous false claims of cell lines that were touted to support T cell development in tissue cultures. Hence, such weak data by Jaleco et al were not considered by me and most other T cell biologists to be a definitive demonstration that Delta-like-1 on a

cell line can promote T cell development. This notion is further underscored by the fact that no one has since published a report confirming that S17-DL1 cell lines can support T cell development.

The inventors, by contrast, used progenitor cells purified from mouse day 14 fetal liver cells, which are known to not contain any immature or mature T cells. Their OP9-DL1 cells induced generation of huge numbers of cells with a high proportion (>50%) of cells expressing all the known markers of immature and mature T cells in about 2 wk. The use of OP9 cannot be considered obvious as OP9 cells were originally generated to facilitate the differentiation of stem cells to various lineages of hematopoietic cells other than macrophages, especially B cells, erythrocytes, and myeloid cells. Since T cells are not one of these lineages, and because a method for in vitro development of T cells was not known at that time, it was not obvious that OP9 was the cell of choice for promoting T cell development.

5. It should be noted that the requirement for Notch signaling for differentiation of progenitor cells into T cells was being described in the literature prior to work by the inventors. The role of Notch on T cell development was first investigated in the mid 1990s, but the real definite understanding did not emerge until 1999 from work by Radtke et al (Immunity, 1999, 10:547-558). Prior to this there was a lot of confusion. Moreover, Notch signaling is complicated by the presence of several ligands and

multiple molecules that regulate Notch interaction to its ligands and its intracellular signaling. Therefore, it is not obvious to use Delta-like-1 on OP9 cells, instead of using other Notch ligands or using one of the Notch signaling modulators.

6. Overall, I strongly feel that production of OP9-DL1 cells by the inventors is novel and inventive. This cell line has survived the test of time and has been the cell line of choice for studying T cell development under in vitro conditions. All other claims of similar feat have disappeared. Many other investigators had desired and attempted to generate a cell line like OP9-DL1, but no one else was able to, including Jaleco et al.

7. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and, further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such a willful false statement may jeopardize the validity of the application or any patent issuing thereon.

January 11, 2009

Date



Charles D. Surh

## CURRICULUM VITAE

**Charles D. Surh**

Office Address: Department of Immunology IMM26  
The Scripps Research Institute  
10550 North Torrey Pines Road  
La Jolla, CA 92037

Office Phone: (858) 784-2006  
Office Fax: (858) 784-8227  
E-mail Address: [csurh@scripps.edu](mailto:csurh@scripps.edu)

Title/Affiliation: Professor  
Department of Immunology  
The Scripps Research Institute

### PERSONAL

Date of Birth: January 30, 1961  
Place of Birth: Seoul, Korea  
Citizenship: U.S.A.  
Marital Status: Married with three children

### EDUCATION

1978 - 1983 B.A., Chemistry, University of California, San Diego, California  
1984 - 1989 Ph. D., Immunology, University of California, Davis, California

### PROFESSIONAL RECORD

1989 - 1992 Postdoctoral Fellow, Department of Immunology,  
The Scripps Research Institute, La Jolla, California.  
Laboratory Head: Dr. Jonathan Sprent

1992 - 1993 Senior Research Associate, Department of Immunology,  
The Scripps Research Institute, La Jolla, California

1993 - 1998 Assistant Professor, Department of Immunology,  
The Scripps Research Institute, La Jolla, California

1998 - 2005 Associate Professor, Department of Immunology,  
The Scripps Research Institute, La Jolla, California

2005 - 2008 Associate Professor with Tenure, Department of Immunology,  
The Scripps Research Institute, La Jolla, California

2008 - present Professor, Department of Immunology,  
The Scripps Research Institute, La Jolla, California

## AWARDS AND HONORS

Student Research Prize from the 39th Annual Meeting of the American Association for the Study of Liver Disease, November 1988

Member of the Biological Science Council representing the graduate students of the University of California, Davis, 1988-1989

Special Fellow, Leukemia Society of America, July 1993 - June 1996

Scholar, The Leukemia and Lymphoma Society, July 1999 - June 2004

Ho-Am Prize in Medicine, 2007

## INVITED PRESENTATIONS (from 1999)

- 04/19/1999 Experimental Biology '99 (FASEB) meeting, Washington, D.C., speaker and co-chair of Block Symposium on T Cell Development
- 09/13/1999 La Jolla Institute for Allergy & Immunology, Seminar Series, San Diego, CA
- 09/30/1999 The Scripps Research Institute, Immunology Affinity Group Seminar Series
- 10/04/1999 University of Washington, Immunology Seminar Series, Seattle, WA
- 10/18/1999 Second International Workshop on Antigen Processing and Presentation, Role of MHC Molecules in Selection and maintenance of T-Cell Repertoire Session, Bar Harbor, Maine
- 01/23/2000 Midwinter Conference of Immunologists at Pacific Grove, California, Differentiation and Cell Death in Lymphocyte Development Session
- 04/07/2000 Walter & Eliza Hall Institute, Melbourne, Australia, Immunology Seminar Series
- 04/11/2000 ThymOz III, an international workshop on T cells, speaker and co-chair at Peripheral T Cells Session
- 05/18/2000 University of British Columbia, Vancouver, Canada, Distinguished Lecture Series
- 05/23/2000 Emory University, Atlanta, Georgia, Immunology Seminar Series
- 05/24/2000 Medical College of Georgia, Augusta, Immunology Seminar Series
- 05/25/2000 NYU Medical Center, New York, NY, Immunology Seminar Series
- 02/20/2001 Gordon Conference on Immunochimistry and Immunobiology, Ventura, California, T cell Homeostasis Session
- 05/15/2001 Transplant 2001, The Joint American Transplant Meeting, Chicago, Illinois, Basic Science Symposium: Immune Regulation
- 07/25/2001 11<sup>th</sup> International Congress of Immunology, Stockholm, Sweden, co-chair of Workshop on Memory T Cells
- 10/23/2001 27<sup>th</sup> Annual Conference of the La Jolla Immunologists, La Jolla, CA, speaker and chair of session on Lymphocyte/Immune Cell Development
- 11/04/2001 ThymUs, an international workshop on T cells, speaker and co-chair of session on T Cell Homeostasis
- 01/26/2002 Midwinter Conference of Immunologists at Pacific Grove, CA, Control of Lymphocyte Survival Session

- 02/08/2002 9<sup>th</sup> International Conference on Lymphocyte Activation and Immune Regulation titled Lymphocyte Traffic and Homeostasis, Newport Beach, CA, Naïve T Cells Session
- 04/20/2002 Experimental Biology 2002 (FASEB) meeting, New Orleans, Louisiana, Major Symposium G on Homeostasis in the Immune System
- 05/20/2002 University of Minnesota at Minneapolis, Minnesota, MICaB Graduate Student Seminar Series
- 07/12/2002 Trudeau Institute, Saranac Lake, New York, Immunology Seminar Series
- 10/15/2002 NIH, Immunology Interest Group Seminar Series
- 12/03/2002 British Society for Immunology Congress, Harrogate, England, Markers for Memory Session
- 01/07/2003 Keystone Symposia: Mechanisms of Immunologic Tolerance and Its Breakdown, Snowbird, Utah, chair of a workshop
- 01/30/2003 Keystone Symposia: Linking Innate with Adaptive Immune Responses, Immune Responses Plenary Session, Taos, NM
- 02/25/2003 Louisiana State University Health Sciences Center, Department of Microbiology, Immunology and Parasitology Seminar Series
- 04/01/2003 ThymOz IV, An International Workshop on T Lymphocytes, Co-chair and speak in T cell selection and Maturation session
- 04/28/2003 Oregon Health & Science University, Portland, OR Immunology Seminar Series
- 05/13/2003 University of Pennsylvania, Immunology Colloquium Series
- 05/15/2003 Yale University, Immunobiology Seminar Series
- 06/28/2003 FASEB Summer Research Conferences on Lymphocytes and the immune system: Molecular, Cellular and Integrative Mechanism, Regulation of Immune Responses session, Tucson, AZ
- 09/10/2003 NIH-Cytokine Interest Group Symposium, Cytokines and Lymphoid Homeostasis.
- 09/24/2003 The University of Iowa, Immunology Seminar Series
- 10/09/2003 The 15<sup>th</sup> Annual Meeting of the Korean Society of Molecular and Cellular Biology, Immunological Memory Symposium, Seoul, Korea
- 10/10/2003 The 33<sup>rd</sup> Annual congress of The Korean Society of Transplantation, , Seoul, Korea
- 11/19/2003 The University of Texas Southwestern Medical Center at Dallas, Excellence in Immunology Lecture Series
- 02/04/2004 10<sup>th</sup> DRDC-IBS Workshop on Stress and Immunity, Autrans, France, Lymphocyte population dynamics session
- 07/18/2004 12<sup>th</sup> International Congress in Immunology, Montreal, Canada, Co-chair and speaker in minisymposium on Lymphoid Homeostasis
- 09/16/2004 UCI Center for Immunology and UCI Cancer Research Institute, UC Irvine, Irvine, CA, Seminars in Immunology series.
- 03/19/2005 Keystone Symposia, Basic Aspects of Tumor Immunology, Keystone, CO, Cytokines and Chemokine session.
- 05/18/2005 Cleveland Clinic Foundation, Cleveland, OH, Department of Immunology Seminar Series.
- 05/22/2005 American Transplant Congress, Seattle, WA, Basic Science Symposium: T Cell Memory and Homeostasis.
- 06/11/2005 FASEB Summer Research Conference on Autoimmunity, Saxton River, VT, Chair and Speaker in Innate Immunity and Dendritic Cells in Autoimmunity Session.



- 09/25/2005 Aegean Conference of Autoimmunity, Santorini, Greece
- 10/27/2005 Frontier in Transplantation, Seoul National University Hospital, Seoul, Korea
- 10/27/2005 International Cytokine Society Conference 2005, Seoul, Korea, Symposium 7: Cytokines and Memories.
- 10/31/2005 Pohang University Seminar Series, Pohang, Korea
- 11/01/2005 Inaugural Symposium for Translational Research Center for Intractable Diseases, Ulsan University Hospital, Ulsan Korea
- 11/07/2005 Charles Gould Easton Seminar series, University of Toronto, Toronto, Canada
- 11/19/2005 Autumn Immunology Conference, Chicago, IL, Tumor Immunology Session
- 11/21/2005 Immunology Seminar Series, The University of Chicago Biomedical Science Cluster
- 03/06/2006 Seminar Series, Intercollegiate Faculty of Nutrition, Texas A & M University, College Station, TX
- 05/03/2006 Immunology Group Seminar Series, University of Maryland, Baltimore, MD
- 06/02/2006 7<sup>th</sup> Elsinore meeting on Infection Immunity, Immune Memory Session, LO-Skolen, Elsinore, Denmark
- 08/12/2006 FASEB Summer Conference in Lymphocytes and Antibodies, T cell homeostasis/memory session, Indian Wells, CA
- 11/08/2006 Symposium on T Cell Memory & Tolerance, POSTECH, Pohang, Korea
- 11/10/2006 Korean Association of Immunologist Conference, Memory T cells Session, Seoul, Korea
- 11/11/2006 Annual Symposium of Transplantation Research Institute, Seoul University, Seoul, Korea
- 02/27/2007 Johnson & Johnson PRD, San Diego, CA
- 03/03/2007 Keystone Symposium on Immunologic Memory, CD4<sup>+</sup> T cell Memory Session, Santa Fe, NM
- 03/28/2007 Keystone Symposium on The potent new Anti-Tumor Immunotherapies, Lymphodepletion Session Chair and Speaker, Banff, Alberta, Canada
- 04/24/2007 Immunology Seminar Series, University of Miami, Miami, FL
- 04/30/2007 Immunology Forum, Dept. of Microbiology, Immunology & Molecular Genetics, David Geffen School of Medicine at UCLA, Los Angeles, CA
- 06/12/2007 Immunology Seminar Series, La Jolla Institute of Allergy and Immunology, La Jolla, CA
- 06/28/2007 SRC Summer Camp, Session on Immune Manipulation, Kang-Neung, Korea
- 08/29/2007 Novo Nordisk AS/ Malov, Denmark
- 10/04/2007 Perspectives in Melanoma XI, Session on Regulation of Immunity: Keys to Melanoma Therapy, Huntington Beach, CA
- 10/28/2007 Keynote Speaker, The Immunology Group of Victoria Annual Retreat, Beechworth, Australia
- 11/06/2007 Symposium on T Cell Memory, POSTECH, Pohang, Korea
- 11/09/2007 Korean Association of Immunologist Conference, Transplantation Session, Seoul, Korea
- 11/10/2007 Annual Forum on Xenotransplantation, Xenotransplantation Center, Seoul National University, Seoul, Korea
- 02/13/2008 Faculty Lecture Series, The Scripps Research Institute, La Jolla, CA

- 04/06/2008 Experimental Biology 2008, American Association of Immunology, Co-Chair of Block Symposium. San Diego, CA
- 06/02/2008 Ho-Am Lecture, Sung Kyun Kwan University, Suwan, Korea
- 08/14/2008 UKC2008, US-Korea Conference on Science and Technology, Chair and Speaker in Cell Signaling Session. San Diego, CA
- 09/03/2008 George Washington University, Microbiology Immunology and Tropical Medicine, Medical Center Dean Seminar Series, Washington, DC
- 09/26/2008 Frontiers in Immunological Memory, Division of Basic & Clinical Immunology, Univ. of Calif. At Irvine, Newport Beach, CA
- 10/23/2008 University of Massachusetts Medical School, Pathology Fall Seminar Series, Worcester, MA
- 11/09/2008 ThymUS, International Conference on Lymphopoiesis, T cell differentiation and Immune Reconstitution, San Juan, Puerto Rico
- 11/12/2008 Human Antibodies & Hybridomas 2008, New York, NY

## JOURNAL RESPONSIBILITIES

- 1993-2005 Associate Editor, The Journal of Immunology
- 2008-2009 Associate Editor, Immunology, Journal of British Immunology Society

Ad hoc reviewer for Science, Nature, Cell, Immunity, Nature Immunology, Nature Medicine, Nature Reviews in Immunology, The Journal of Experimental Medicine, Proceedings of National Academy of Science, Journal of Immunology, Journal of Clinical Investigation, Blood and European Journal of Immunology

## PROFESSIONAL ACTIVITIES

- 02/08/1998 Site Visit for NCI program project review, Seattle, WA
- 1999-2001 Study section grant review – American Heart Association, National Review Committee
- 04/12/2002 Special Emphasis Panel, Immunological Sciences Study Section, grant review, National Institutes of Health
- 2002-2003 Organizing committee for Annual La Jolla Immunology Conference
- 2003-2008 Science Advisory Board member for Xenotransplantation Research Center, Seoul National University Hospital, Seoul, Korea
- 09/12/2004 Site Visit, Laboratory of Mammalian Genes and Development, NICHD, NIH, Bethesda, MD
- 2004-2007 Science Advisory Committee member for Center for Children's Environmental Health, UC Davis, Davis, CA
- 2006-present Committee that on evaluation new mutant mouse strains for repository, NIAID, NIH, Bethesda, MD

October, 2006	Ad hoc reviewer for CMI-B Study Section, NIH, Bethesda, MD
2006-2008	Chair of Immunology Affinity Group, TSRI
2004-2008	Scientific Committee for ThymUS'08, International Conference on Lymphopoiesis, T cell differentiation and Immune Reconstitution

## TEACHING ACTIVITIES

07/23/2005	AAI Advanced Immunology Course, Stanford University, CA, Lecture on T Lymphocyte Homeostasis and Memory
07/20/2006	AAI Advanced Immunology Course, Stanford University, CA, Lecture on T Lymphocyte Homeostasis and Memory.
2007-	Participate in teaching the Immunobiology Course at TSRI Graduate program
07-08/2007	Teach a special 6-week Advance Immunology Course at POSTECH, Pohang, Korea
07-08/2007	Lecture at weekly faculty T-cell Meeting at Seoul National University, Seoul, Korea

## PATENTS

Methods for increasing the biological Activity of Cytokines or Lymphokines for treatment of disease in a mammalian subject. PTC International Application filed 08/13/2008

## CURRENT PERSONNEL

Jared Purton, Ph.D.  
08/01/03-present  
Previous position: Graduate Student  
Monash University, Melbourne, Australia

Ester M.M. van Leeuwen, Ph.D.  
03/12/06 – present  
Previous position: Graduate Student  
University of Amsterdam, Amsterdam,  
The Netherlands

Mee Kum Kim, M.D.  
03/2008 – present  
Visiting Scientist from  
Seoul National University Medical School  
Seoul, Korea

Joonyoub Lee  
05/01/04-present  
Graduate Student, TSRI

Chris Martin  
05/01/2007-present  
Graduate Student, TSRI

David Kim  
06/01/2003-present  
Technician

## **PAST TRAINEES**

Ted Burgardt  
Technician  
Current position: Veterinary school

Jennifer M. Chang  
Undergraduate student, UCSD/Scientific Intern  
Current position: Graduate Student  
University of California, Berkeley

Walter L.S. Chang  
Undergraduate student, UCSD/Scientific Intern  
Current position: Medical School

Zhaoqing Ding  
High School Student/Scientific Intern  
Current Position: Graduate Student  
Stanford Univeristy, Stanford, CA

Wolfgang Dummer, M.D.  
Postdoctoral Fellow  
Current position: Staff Scientist  
Genentech, Inc.  
South San Francisco, California

Bettina B. Ernst, Ph.D.  
Postdoctoral Fellow  
Laboratory Manager  
UMNW, ETH  
Zurich, Switzerland

William Chad Kieper, Ph.D.  
Postdoctoral fellow  
Current position: Sr. Immunologist  
3M Pharmaceuticals  
St. Paul, Minnesota

Dong-Sup Lee, M.D., Ph.D.  
Postdoctoral Fellow  
Current position: Assistant Professor  
Seoul National University  
Seoul, Korea

Jung Won Min  
Undergraduate student, UCSD/Scientific Intern  
Current position: Science Teacher  
Twin Peaks Middle School  
Poway, CA

Chris Ramsey, Ph.D.  
Postdoctoral fellow  
Current position: Adjunct Professor  
Moorpark College, Moorpark CA

Joyce Tsi Tan, Ph.D.  
Postdoctoral fellow  
Current position: Scientist  
Pfizer, Inc  
San Diego, CA

Kien Vuu  
Undergraduate student, UCSD/Scientific Intern  
Current position: Resident in Radiology  
University of California, Los Angeles

#### **PUBLICATIONS** (excluding abstracts)

1. Glassy, M. C., C. D. Surh, and S. Sarkar. Murine monoclonal antibodies that identify antigenically distinct subpopulations of human sperm. *Hybridoma* 3:363-371 (1984).
2. Glassy, M. C. and C. D. Surh. Immunodetection of cell-bound antigens using both mouse and human monoclonal antibodies. *J. Immunol. Methods* 81:115-122 (1985).
3. Gaffar, S. A., C. D. Surh, and M. C. Glassy. Variations in the secretion of monoclonal antibodies by human-human hybridomas. *Hybridoma* 5:93-105 (1986).
4. Glassy, M.C., H. H. Handley, C. D. Surh, and I. Royston. Genetically stable human hybridomas secreting tumor-reactive human monoclonal IgM. *Cancer Investigation* 5:449-457 (1987).

5. Surh, C. D., M. E. Gershwin, and A. Ahmed. A peripheral and central T cell antigen recognized by a monoclonal thymocytotoxic autoantibody from New Zealand black mice. *J. Immunol.* 138:1421-1428 (1987).
6. Surh, C. D., A. E. Cooper, R. L. Coppel, P. Leung, A. Ahmed, R. Dickson, and M. E. Gershwin. The predominance of IgG3 and IgM isotype antimitochondrial autoantibodies against recombinant fused mitochondrial polypeptide in patients with primary biliary cirrhosis. *Hepatology* 8:290-295 (1988).
7. Coppel, R. L., L. J. McNeilage, C. D. Surh, J. Van de Water, T. W. Spithill, S. Whittingham, and M. E. Gershwin. Primary structure of the human M2 mitochondrial autoantigen of primary biliary cirrhosis: dihydrolipoamide acetyltransferase. *Proc. Natl. Acad. Sci.* 85:7317-7321 (1988).
8. Surh, C. D., A. Ansari, and M. E. Gershwin. In vitro functional characterization of SAG-3 - A naturally occurring monoclonal antibody in NZB mice: specificity towards functional T cell subsets. *Hybridoma* 7:609-625 (1989).
9. Surh, C. D., D. J. Danner, A. Ahmed, R. L. Coppel, I. R. Mackay, R. Dickson, and M. E. Gershwin. Reactivity of primary biliary cirrhosis sera with a human fetal liver cDNA clone of branched alpha-keto acid dehydrogenase dihydrolipoamide acyltransferase, the 52 kD mitochondrial autoantigen. *Hepatology* 9:63-68 (1989).
10. Krams, S. M., C. D. Surh, R. L. Coppel, A. Ansari, B. Ruebner, and M. E. Gershwin. Immunization of experimental animals with dihydrolipoamide acetyltransferase, as a purified recombinant polypeptide, generates mitochondrial autoantibodies but not primary biliary cirrhosis. *Hepatology* 9:411-416 (1989).
11. Van de Water, J., C. D. Surh, P. S. C. Leung, S. M. Krams, D. R. Fregeau, P. Davis, R. Coppel, I. Mackay and M. E. Gershwin. Molecular definitions, autoepitopes and enzymatic activities of the mitochondrial autoantigens of primary biliary cirrhosis. *Sem. Liver Dis.* 9(2):132-137 (1989).
12. Van de Water, J., A. Cooper, C. D. Surh, D. J. Danner, R. L. Coppel, R. Dickson, and M. E. Gershwin. Detection of autoantibodies to recombinant mitochondrial proteins in patients with primary biliary cirrhosis. *New Eng. J. Med.* 320:1377-1380 (1989).
13. Surh, C. D., T. E. Roche, D. J. Danner, A. A. Ansari, R. L. Coppel, R. Dickson, and M. E. Gershwin. Antimitochondrial autoantibodies in primary biliary cirrhosis recognize cross-reactive epitope(s) on protein X and dihydrolipoamide acetyltransferase of pyruvate dehydrogenase complex. *Hepatology* 10:127-133 (1989).
14. Surh, C. D., A. A. Ansari and M. E. Gershwin. Comparative epitope mapping of murine monoclonal and human autoantibodies to human PDH-E2, the major mitochondrial autoantigen of primary biliary cirrhosis. *J. Immunol.* 144:2647-2652 (1990).

15. Surh, C. D., R. Coppel and M. E. Gershwin. Structural requirement for auto-reactivity on human pyruvate dehydrogenase-E2, the major autoantigen of primary biliary cirrhosis: implication for a conformational epitope. *J. Immunol.* 144:3367-3374 (1990).
16. Van de Water, J., A. A. Ansari, C. D. Surh, R. Coppel, T. Roche, H. Bonkovsky, M. Kaplan and M. E. Gershwin. Evidence for the targeting by 2-oxo-dehydrogenase enzymes in the T cell response of primary biliary cirrhosis. *J. Immunol.* 146: 89-94 (1991).
17. Agus, D. B., C. D. Surh, and J. Sprent. Reentry of T cells to the adult thymus is restricted to activated T cells. *J. Exp. Med.* 173:1039-1046 (1991).
18. Karlsson, L., C. D. Surh, J. Sprent, and P. A. Peterson. A novel class II MHC molecule with unusual tissue distribution. *Nature* 351:485 (1991).
19. Gao, E. K., H. Kosaka, C. D. Surh, and J. Sprent. T cells contact with Ia antigens on nonhemopoietic cells in vivo can lead to immunity rather than tolerance. *J. Exp. Med.* 174:435-446 (1991).
20. Sprent, J., M. Schaefer, M. Hurd, C. D. Surh, and Y. Ron. Mature murine B and T cells transferred to SCID mice can survive indefinitely and many maintain a virgin phenotype. *J. Exp. Med.* 174:717-728 (1991).
21. Surh, C. D. and J. Sprent. Long-term xenogeneic chimeras: Full differentiation of rat T and B cells in SCID mice. *J. Immunol.* 147:2148-2154 (1991).
22. Frey, H. B. Ernst, C. D. Surh, and J. Sprent. Thymus-grafted SCID mice show transient thymopoiesis and limited depletion of V $\beta$ 11<sup>+</sup> T cells. *J. Exp. Med.* 175:1067-1071(1992).
23. Surh, C. D., E. K. Gao, H. Kosaka, D. Lo, C. Ahn, D. Murphy, L. Karlsson, P. Peterson, and J. Sprent. Two subsets of epithelial cells in the thymic medulla. *J. Exp. Med.* 176:495-505 (1992).
24. Surh, C. D., B. Ernst, and J. Sprent. The growth of epithelial cells in the thymic medulla is under the control of mature T cells. *J. Exp. Med.* 176:611-616 (1992).
25. Kosaka, H., C. D. Surh, and J. Sprent. Stimulation of mature unprimed CD8<sup>+</sup> T cells by semi-professional APC in vivo. *J. Exp. Med.* 176:1291-1302(1992).
26. Karlsson, L., C. D. Surh, J. Sprent, and P. A. Peterson. An unusual class II molecule. *Immunology Today* 13:469-470(1992).
27. Leung, P.S., S. Krams, S. Munoz, C. D. Surh, A. Ansari, T. Kenny, D. L. Robbins, J. Fung, T. E. Starzl, W. Maddrey, R. L. Coppel, and M. E. Gershwin. Characterization and epitope mapping of human monoclonal antibodies to PDC-E2, the

immunodominant autoantigen of primary biliary cirrhosis. *J. Autoimmunity* 5:703-718(1992).

28. Surh, C. D., J. Sprent, and S. R. Webb. Exclusion of circulating T cells from the thymus does not apply in the neonatal period. *J. Exp. Med.* 177:379-385(1993).
29. Van de Water, J., J. Turchany, P. S. C. Leung, J. Lake, S. Munoz, C. D. Surh, R. Coppel, A. A. Ansari, Y. Nakanuma, and M. E. Gershwin. Molecular mimicry in primary biliary cirrhosis: evendence for biliary epithelial expression of protein crossreactive with PDC-E2. *J. Clin. Invest.* 91:2653-2664(1993).
30. Sprent, J., H. Kosaka, E.-K. Gao, C. D. Surh, and S. R. Webb. Intrathymic and extrathymic tolerance in bone marrow chimeras. *Immunol. Rev.* 133:151-176(1993).
31. Surh, C. D. and J. Sprent. Anatomy and histology of the thymus. In: Intrathymic Development of T cells, J. Nikolic-Zugic ed., R. G. Landes Co., TX, pp3-27 (1994).
32. Surh, C. D., D. P. Gold, S. Wiley, D. B. Wilson, and J. Sprent. Rat T cell response to superantigens. I. V $\beta$ -restricted clonal deletion of rat T cells differentiating in rat  $\rightarrow$  mouse chimeras. *J. Exp. Med.* 179:57-62 (1994).
33. Gold, D. P., C. D. Surh, K. S. Sellins, K. Schroder, J. Sprent, and D. B. Wilson. Rat T cell response to superantigens. II. Allelic differences in V $\beta$ 8.2 and V $\beta$ 8.5  $\beta$  chains determine responsiveness to staphylococcal enterotoxin B and mouse mammary tumor virus encoded products. *J. Exp. Med.* 179:63-69 (1994).
34. Degermann, S., C. D. Surh, L. H. Glimcher, J. Sprent, and D. Lo. B7 expression on thymic medullary epithelium correlates with epithelium mediated deletion of V $\beta$ 5<sup>+</sup> thymocytes. *J. Immunol.* 152:3254-3263 (1994).
35. Sprent, J., H. Kosaka, and C. D. Surh. Tolerogenicity of thymic epithelial cells: studies with allogeneic and xenogeneic chimeras. In: *Rejection and Tolerance*, J. L. Touraine, et al. eds., Kluwer Academic Publishers, Netherlands. pp125-140 (1994).
36. Sprent, J., C. D. Surh, D. Agus, M. Hurd, S. Sutton, and W. R. Heath. Profound atrophy of the bone marrow reflecting major histocompatibility complex class II-restricted destruction of stem cells by CD4<sup>+</sup> cells. *J. Exp. Med.* 180:307-317 (1994).
37. Sprent, J., C. D. Surh, and D. Tough. Fate of T and B cells transferred to SCID mice. *Res. Immunol.* 145(5):328- (1994).
38. \*Surh, C. D. and J. Sprent. T-cell apoptosis detected in situ during positive and negative selection in the thymus. *Nature*, 372:100-103 (1994).



39. Kishimoto, H., C. D. Surh, and J. Sprent. Upregulation of surface markers on dying thymocytes. *J. Exp. Med.* 181:649-655 (1995).
40. Surh, C. D. T cell death in the thymus during thymic selection. *J. NIH Res.* 7:56-57 (1995).
41. Ernst, B., C. D. Surh, and J. Sprent. Thymic selection and cell division. *J. Exp. Med.* 182:961-972 (1995).
42. Surh, C. D., H. Kishimoto, and J. Sprent. Flow cytometric quantitation of apoptotic cells using TUNEL and In situ detection of apoptotic cells in tissue sections by TUNEL. *Curr. Protocol Immunol.* Section 3.17 (1995).
43. Fung-Leung, W.-P., C. D. Surh, M. Jiljedahl, J. Pang, D. Leturcq, P. A. Peterson, S. R. Webb, and L. Karlsson. Antigen presentation and T cell development in H2-M-deficient mice. *Science* 271:1278-1281 (1996).
44. Ernst, B., C. D. Surh, and J. Sprent. Bone-marrow-derived cells fail to induce positive selection in thymus reaggregation cultures. *J. Exp. Med.* 183:1235-1240 (1996).
45. Oehen, S., L. Feng, Y. Xia, C. D. Surh, and S. M. Hedrick. Antigen compartmentation and helper T cell tolerance induction. *J. Exp. Med.* 183:2617-2626 (1996).
46. Song, E. S., V. Lee, C. D. Surh, A. Lynn, D. Brumm, D. J. Jolly, J. F. Warner, and S. Chada. Antigen presentation in retroviral mediated gene transfer in vivo. *Proc. Natl. Acad. Sci.* 94:1943-1948 (1997).
47. Surh, C. D., H. Kosaka, and J. Sprent. Rat stem cells developing in irradiated SCID mice fail to become tolerized and cause lethal graft-versus-host disease. *Am. J. Pathol.* 151:591-599 (1997).
48. Surh, C. D., D.-S. Lee, W.-P. Fung-Leung, L. Karlsson and J. Sprent. Thymic selection by a single MHC/peptide ligand produces a semi-diverse repertoire of CD4<sup>+</sup> T cells. *Immunity* 7:209-219 (1997).
49. Kishimoto, H., C. D. Surh and J. Sprent. A role for fas in negative selection of thymocytes in vivo. *J. Exp. Med.* 184:1427-1438 (1998).
50. Liljedahl, M., O. Winqvist, C. D. Surh, P. Wong, K. Ngo, L. Teyton, P. A. Peterson, A. Brunmark, A.Y. Rudensky, W. P. Fung-Leung, L. Karlsson. Altered antigen presentation in mice lacking H2-O. *Immunity* 8:233-243 (1998).
51. Surh, C. D. and J. Sprent. The thymus and T cell development. In: *Inflammation: Basic Principles and Clinical Correlates*, J. I. Gallin and R. Snyderman Eds., Chapter 9, pp. 137-149 (1999).

52. Lee, D.-S., C. Ahn, B. Ernst, J. Sprent and C. D. Surh. Thymic selection by a single MHC/peptide ligand: autoreactive T cells are low affinity cells. *Immunity* 10:83-92 (1999).
- 53\*. Ernst, B., D.-S. Lee, J. M. Chang, J. Sprent and C. D. Surh. The peptide ligands mediating positive selection in the thymus control T cell survival and homeostatic proliferation in the periphery. *Immunity* 11:173-181 (1999).
54. Anderson, K. L., H. Perkin, C. D. Surh, S. Venturini, R. A. Maki, and B. E. Torbett. Transcription factor PU.1 is necessary for development of thymic and myeloid progenitor-derived dendritic cells. *J. Immunol.* 164:1855-1861 (2000).
55. Hwang, I, J. F. Huang., H. Kishimoto, A. Brunmark, P. A. Peterson, M.R. Jackson, C. D. Surh, Z. Cai, and J. Sprent. T cells can use either T cell receptor or CD28 receptors to absorb and internalize cell surface molecules derived from antigen-presenting cells. *J. Exp. Med.* 191:1137-48, (2000).
56. Surh, C. D., B. Ernst, D.-S. Lee, W. Dummer, and E. LeRoy. Role of self-major histocompatibility complex/peptide ligands in selection and maintenance of a diverse T cell repertoire. *Immunol. Res.* 21/2-3:331-339 (2000).
57. Surh, C. D. and J. Sprent. Homeostatic T Cell Proliferation. How far can T cells be activated to self-ligands? *J. Exp. Med.* 192:F9-F14 (2000).
58. Dummer, W., B. Ernst, E. LeRoy, D.-S. Lee, and C. D. Surh. Autologous regulation of naïve T cell homeostasis within the T cell compartment. *J. Immunol.* 166:2460-2468 (2001).
59. Sprent, J. and C. D. Surh. Generation and maintenance of memory T cells. *Curr. Opin. Immunol.* 13:248-254 (2001).
- 60\*. Tan, J.T., E. Dudl, E. LeRoy, R. Murray, J. Sprent, K.I. Weinberg, and C. D. Surh. IL-7 is critical for homeostatic proliferation and survival of naïve T cells. *Proc. Natl. Acad. Sci. USA* 98:8732-7 (2001).
61. Ostler, T., T. Hussell, C.D. Surh, P. Openshaw, and S. Ehl. Long-term persistence and reactivation of T cell memory in the lung of mice infected with respiratory syncytial virus. *Eur. J. Immunol.* 31:2574-82 (2001).
62. Gapin, L., J.L. Matsuda, C.D. Surh, and M. Kronenberg. NKT cells derive from double-positive thymocytes that are positively selected by CD1d. *Nat. Immunol.* 2:971-8 (2001).
63. Surh, C.D. and J. Sprent. Regulation of naïve and memory T cell homeostasis. *Microbes and Infection*, 4:51-6 (2002).
64. Zhang, X., H. Fujii, H. Kishimoto, E. LeRoy, C.D. Surh, and J. Sprent. Aging leads to disturbed homeostasis of memory phenotype CD8<sup>+</sup> cells. *J. Exp. Med.* 195:283-93 (2002).

65. Sprent, J. and C.D.Surh. T cell memory. *Annu. Rev. Immunol.* 20:551-79 (2002).
- 66\*. Tan, J.T., B. Ernst, W.C. Kieper, E. LeRoy, J. Sprent, and C.D. Surh. Interleukin (IL)-15 and IL-7 jointly regulate homeostatic proliferation of memory phenotype CD8<sup>+</sup> cells but are not required for memory phenotype CD4<sup>+</sup> cells. *J. Exp. Med.* 195:1523-1532 (2002).
67. Kieper, W.C., J.T. Tan, B. Bondi-Boyd, L. Gapin, J. Sprent, R. Ceredig, and C.D. Surh. Overexpression of interleukin (IL)-7 leads to IL-15-independent generation of memory phenotype CD8<sup>+</sup> T cells. *J. Exp. Med.* 195:1533-1539 (2002).
68. Matsuda J.L., L. Gapin, S. Sidobre, W. C. Kieper, J. T. Tan, R. Ceredig, C. D. Surh, M. Kronenberg. Homeostasis of V $\alpha$ 14i NKT cells. *Nat. Immunol.* 3:966-74 (2002).
69. Judge A.D., X. Zhang, H. Fujii, C.D. Surh, and J. Sprent. Interleukin 15 Controls both Proliferation and Survival of a Subset of Memory-Phenotype CD8<sup>+</sup> T Cells. *J. Exp. Med.* 196:935-46 (2002).
70. Surh CD, Tan J, Kieper WC, Ernst B. Factors regulating naive T cell homeostasis. *Adv Exp Med Biol.* 512:73-80 (2002).
71. Sprent J, Surh CD. Cytokines and T cell homeostasis. *Immunol Lett.* 22;85(2):145-9 (2003).
72. Sprent J, Surh CD. Knowing one's self: central tolerance revisited. *Nat Immunol.* 4:303-4 (2003).
73. Rosen H, Alfonso C, Surh CD, McHeyzer-Williams MG. Rapid induction of medullary thymocyte phenotypic maturation and inhibition of thymic egress at low nanomolar concentrations of sphingosine 1-phosphate receptor agonist. *Proc. Natl. Acad. Sci.* 100(19):10907-12 (2003).
74. Kaech SM, Tan JT, Wherry EJ, Konieczny BT, Surh CD, Ahmed, R. Selective expression of interleukin 7 receptor identifies effector CD8 T cells that give rise to long-lived memory cells. *Nat. Immunol.* 4(12):1191-8 (2003).
75. Kondrack RM, Harbertson J, Tan J, McBreen ME, Surh CD, Bradley LM. Interleukin 7 regulates the survival and generation of memory CD4 cells. *J. Exp. Med.* 198(12):1797-806 (2003).
76. Kieper WC, Burghardt JT, Surh CD. A role for TCR affinity in regulating naïve T cell homeostasis. *J. Immunol.* 172:40-44 (2004).
77. Kieper WC, Troy A, Burghardt JT, Ramsey C., Lee JY, Jiang H-Q, Dummer W, Shen H, Cebra JJ, Surh CD. Cutting Edge: Recent immune status determines the source of antigens that drive homeostatic T cell expansion. *J Immunol.* 174:3158-63 (2005).

78. Baccala R, Witherden D, Gonzalez-Quintal R, Dummer W, Surh CD, Havran WL, Theofilopoulos AN. Gamma delta T cell homeostasis is controlled by IL-7 and IL-15 together with subset-specific factors. *J Immunol.* 174:4606-12 (2005).
79. Surh CD, Sprent J. Regulation of mature T cell homeostasis. *Semin Immunol.* 17:183-91 (2005).
80. Gattinoni L, Finkelstein SE, Klebanoff CA, Antony PA, Palmer DC, Spiess PJ, Hwang LN, Yu Z, Wrzesinski C, Heimann DM, Surh CD, Rosenberg SA, Restifo NP. Removal of homeostatic cytokine links by lymphodepletion enhances the efficacy of adoptively transferred tumor-specific CD8<sup>+</sup> T cells. *J. Exp. Med.* 202:907-912 (2005).
81. Davey GM, Starr R, Cornish AL, Burghardt T, Alexander WS, Carbone FR, Surh CD, Heath WR. SOCS-1 regulates IL-15-driven homeostatic proliferation of antigen-naïve CD8 T cells, limiting their autoimmune potential. *J. Exp. Med.* 202:1099-108 (2005).
82. Lee SK, Surh CD. Role of interleukin-7 in bone and T-cell homeostasis. *Immunol. Rev.* 208:169-80 (2005).
83. Ramsey C, Hässler S, Marits P, Kämpe O, Surh CD, Peltonen L, Winqvist O. Increased antigen presenting cell mediated T-cell activation in mice and patients missing the autoimmune regulator. *Eur. J. Immunol.* 36:305 (2006).
84. Boyman O, Kovar M, Rubinstein MP, Surh CD, Sprent J. Selective stimulation of T cell subsets with antibody-cytokine immune complexes. *Science* 311:1924-7 (2006).
85. Surh CD, Sprent J. On the TRAIL of homeostatic memory T cells. *Nat. Immunol.* 7:439-41 (2006).
86. Rubinstein MP, Kovar M, Purton JF, Cho JH, Boyman O, Surh CD, Sprent J. Converting IL-15 to a superagonist by binding to soluble IL-15Ralpha. *Proc Natl Acad Sci U S A.* 103:9166-71. (2006)
87. Boyman O, Cho JH, Tan JT, Surh CD, Sprent J. A major histocompatibility complex class I-dependent subset of memory phenotype CD8<sup>+</sup> cells. *J Exp Med.* 203:1817-25 (2006).
88. Surh CD, Boyman O, Purton JF, Sprent J. Homeostasis of memory T cells. *Immunol Rev.* 211:154-63 (2006).
89. McKay D, Shigeoka A, Rubinstein M, Surh C, Sprent J. Simultaneous deletion of MyD88 and Trif delays major histocompatibility and minor antigen mismatch allograft rejection. *Eur J Immunol.* 36:1994-2002 (2006).
90. Tan JT, Surh CD. T cell memory. *Current Topics in Microbiology and Immunology*. Pulendran, B and Ahmed, R (Eds). 311:85-115 (2006).

91. Boyman O, Surh CD, Sprent J. Potential use of IL-2/anti-IL-2 antibody immune complexes for the treatment of cancer and autoimmune disease. *Expert Opin Biol Ther*. 6:1323-31. (2006)
- 92.\* Purton JF, Tan JT, Rubinstein MP, Kim DM, Sprent J, Surh CD. Anti-viral CD4<sup>+</sup> memory T cells are IL-15 dependent. *J Exp Med*. 204:951-61 (2007).
92. Boyman O, Purton JF, Surh CD, Sprent J. Cytokines and T-cell homeostasis. *Curr Opin Immunol*. 19:320-6 (2007).
93. Hanick NA, Rickert M, Varani L, Bankovich AJ, Cochran JR, Kim DM, Surh CD, Garcia KC. Elucidation of the Interleukin-15 Binding Site on Its Alpha Receptor by NMR. *Biochemistry*. 46:9453-9461 (2007).
94. Cho JH, Boyman O, Kim HO, Hahm B, Rubinstein MP, Surh CD, Sprent J. An intense form of homeostatic proliferation of naive CD8<sup>+</sup> cells driven by IL-2. *J Exp Med*. 204:1787-801 (2007).
95. Purton JF, Sprent J, Surh CD. Commentary: Staying alive – naïve CD4<sup>+</sup> T cell homeostasis. *Eur J Immunol*. 37: 2367-9 (2007).
96. Lee S, Chung J, Ha IS, Yi K, Lee JE, Kang HG, Choi I, Oh KH, Kim JY, Surh CD, Ahn C. Hydrogen peroxide increases human leukocyte adhesion to porcine aortic endothelial cells via NF{ $\kappa$ }B-dependent up-regulation of VCAM-1. *Int Immunol*. 19(12):1349-59 (2007).
97. Ramsey C, Rubinstein MP, Kim DM, Cho JH, Sprent J, Surh CD. The lymphopenic environment of CD132 ( $\gamma_c$ )-deficient hosts elicits rapid homeostatic proliferation of naïve T cells via IL-15. *J. Immunol*. 180:5320-6 (2008).
98. Sprent J, Cho JH, Boyman O, Surh CD. T cell homeostasis. *Immunol Cell Biol*. 86:385-386 (2008).
99. Boyman O, Ramsey C, Kim K, Sprent J, and Surh CD. IL-7/anti-IL-7 mAb complexes restore T cell development and induce homeostatic T cell expansion without lymphopenia. *J. Immunol*. 180:7265-75 (2008).
100. Bayer AL, Lee JY, de la Barrera A, Surh CD, Malek TR. A function for IL-7R for CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> T regulatory cells. *J. Immunol*. 181:225-34 (2008).
101. Rubinstein MP, Lind NA, Purton JF, Filippou P, Best JA, McGhee PA, Surh CD, Goldrath AW. IL-7 and IL-15 differentially regulate CD8<sup>+</sup> T cell subsets during contraction of the immune response. *Blood*. 2008 Nov 1;112(9):3704-12. Epub 2008 Aug 8
102. Verdeil G, Marquardt K, Surh CD, Sherman LA. Adjuvants targeting innate and adaptive immunity synergize to enhance tumor immunotherapy. *Proc Natl Acad Sci U S A*. 105(43):16683-8 (2008)

103. Sprent J, Surh CD. Re-entry of mature T cells to the thymus: an epiphenomenon? *Immunol Cell Biol*. 2008 Dec 2. [Epub ahead of print]
104. Surh CD, Sprent J. Homeostasis of naïve and memory T cells. *Immunity* 29:848-862 (2008).
105. Lee JY, Ding Z, Kobuley DE, Kim DM, Purton JF, Ahn C, Sprent J, Cebra JJ, Yu Y, Surh CD. Foreign antigens induce the bulk of spontaneous regulatory T cell proliferation in chronically lymphopenic hosts. In review.
- 106.